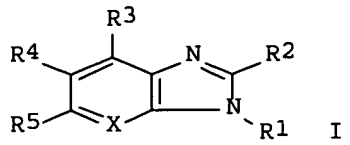
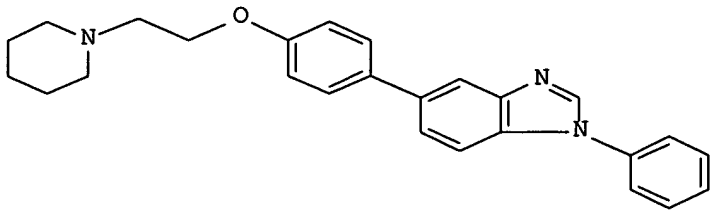
STN SEARCH **10/664,421**

FILE 'HOME' ENTERED AT 07:25:17 ON 23 MAY 2006

```
=> file medline, Caplus
=> s benzimidazol and kinase and inhibitor
L1          14 FILE MEDLINE
L2         158 FILE CAPLUS

TOTAL FOR ALL FILES
L3         172 BENZIMIDAZOL AND KINASE AND INHIBITOR

=> s l3 not 2003-2006/py
L4           7 FILE MEDLINE
L5           8 FILE CAPLUS

TOTAL FOR ALL FILES
L6          15 L3 NOT 2003-2006/PY

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7          10 DUP REM L6 (5 DUPLICATES REMOVED)

=> d ibib abs 1-10

L7   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2002:790223  CAPLUS Full-text
DOCUMENT NUMBER:         137:310915
TITLE:                   Preparation of benzimidazole and imidazopyridine
                         derivatives as angiogenesis inhibitors
INVENTOR(S):             Bilodeau, Mark T.; Hungate, Randall W.; Cunningham,
                         April M.; Koester, Timothy J.
PATENT ASSIGNEE(S):      Merck & Co., Inc., USA
SOURCE:                  U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 143,881,
                         abandoned.
                         CODEN: USXXAM
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  4
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
     US 6465484           B1    20021015    US 2001-786004         20010228
     WO 2000012089        A1    20000309    WO 1999-US5297         19990311
         W:  AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD,
             GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV,
             MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       US 1997-60151P      P  19970926
                                             US 1998-143881      B2 19980831
                                             WO 1999-US5297      W  19990311
OTHER SOURCE(S):         MARPAT 137:310915
GI
```



I



II

AB Title compds. I [X = N; R1 = aryl, heterocyclyl, heteroaryl; R2-3, R5 = H, alkyl; R4 = H, alkyl] were prepared For instance, 1-Bromo-4-fluoro-3- nitrobenzene was reacted with aniline (NMP, i-Pr2NEt, 120°, 14 h), the product coupled to 4-methoxyboronic acid (dioxane/water, Na2CO3, [PPh3]4Pd, 80°, 14 h) and the biaryl reduced (EtOH/HOAc, Pd/C-H2, 2 h) and the resulting intermediate treated with (MeO)3CH at 120° for 30 min to afford 1-phenyl-5-(4-methoxyphenyl)benzimidazole. This was demethylated (CH3CN/CH2Cl2, AlCl3, NaI, reflux, 44 h) and the resulting phenol reacted with 1-(2-chloroethyl)piperidine hydrochloride (DMF, Cs2CO3, 50°) to give II. Compds. of the invention inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 150-650 nM. I are useful for the treatment of tyrosine kinase-dependent diseases/conditions such as angiogenenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2002690151 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12451114
TITLE: Prolonged activation of Ca2+-activated K+ current contributes to the long-lasting refractory period of Aplysia bag cell neurons.
AUTHOR: Zhang Yalan; Magoski Neil S; Kaczmarek Leonard K
CORPORATE SOURCE: Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06520, USA.
CONTRACT NUMBER: NS 18492 (NINDS)
SOURCE: The Journal of neuroscience : the official journal of the Society for Neuroscience, (2002 Dec 1) Vol. 22, No. 23, pp. 10134-41.
Journal code: 8102140. E-ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 14 Dec 2002
Last Updated on STN: 27 Dec 2002
Entered Medline: 23 Dec 2002

AB Stimulation of the bag cell neurons of Aplysia activates several biochemical pathways, including protein kinase C (PKC), and alters their excitability for many hours. After an approximately 30 min afterdischarge, these neurons enter an approximately 18 hr inhibited state during which additional stimulation fails to evoke discharges. In vivo, this refractory period limits the frequency of reproductive behaviors associated with egg laying. We have now examined the role of Ca2+-activated K+ (BK) currents in the refractory period. Outward currents gated by both intracellular Ca2+ and depolarization, with pharmacological characteristics of BK currents, were recorded in isolated bag cell neurons. These currents were enhanced by the BK channel activators phloretin and 1,3-

dihydro-1-[2-hydroxy-5-(trifluoro- methyl)phenyl]-5-trifluoromethyl-2H-benzimidazol-2-one and inhibited by the BK blocker paxilline. The BK component of K+ current was enhanced by 12-O-tetradecanoyl-phorbol-13-acetate, an activator of PKC, and this effect was blocked by sphinganine and PKC(19-36), inhibitors of PKC in bag cell neurons. To test whether the BK current is altered during the refractory period, intact clusters were stimulated to afterdischarge, and neurons were isolated after the clusters had entered the refractory period. Compared with unstimulated cells, current density was almost doubled in refractory neurons. This increase in current was inhibited by preincubating clusters in sphinganine. Treatment of refractory clusters with paxilline significantly restored the ability of stimulation to evoke afterdischarges. Conversely, application of phloretin to previously unstimulated clusters inhibited the onset of afterdischarges. These results indicate that a prolonged increase in BK channel activity contributes to the prolonged refractory period of the bag cell neurons.

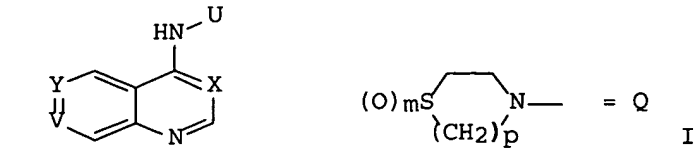
L7 ANSWER 3 OF 10 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002355457 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12020691
TITLE: Cyclic AMP-independent relaxation mediated by beta3-adrenoceptors on guinea pig gastrointestine.
AUTHOR: Horinouchi Takahiro; Koike Katsuo
CORPORATE SOURCE: Department of Chemical Pharmacology, Toho University School of Pharmaceutical Sciences, 2-2-1 Miyama, Funabashi, Chiba, Japan.
SOURCE: European journal of pharmacology, (2002 May 3) Vol. 442, No. 1-2, pp. 137-46.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 9 Jul 2002
Last Updated on STN: 10 Oct 2002
Entered Medline: 8 Oct 2002

AB In this study, we investigated the signal transduction pathway involved in beta(3)-adrenoceptor-mediated relaxations of guinea pig gastric fundus and duodenum. In the presence of beta1- and beta2-adrenoceptor blockade, the potency (pD2 value) of catecholamines ((-)-isoprenaline, (-)-noradrenaline and (-)-adrenaline) and beta(3)-adrenoceptor agonists ((R*, R*)-(+/-)-4-[2-[(2-(3-chlorophenyl)-2-hydroxyethyl)amino]propyl]phenoxyace tic acid sodium (BRL37344) and (+/-)-[4-[3-[(1,1-dimethylethyl)amino]-2- hydroxypropoxy]-1,3-dihydro-2H-benzimidazol-2-one] hydrochloride ((+/-)-CGP12177A)) to induce relaxation was not affected by the adenylate cyclase inhibitor, 9-(tetrahydro-2-furanyl)-9H-purin-6-amine (SQ-22,536, 100 microM). Catecholamines induced an elevation of cyclic AMP and SQ-22,536 significantly abolished the responses of gastric fundus. However, cyclic AMP levels were unaltered by the beta3-adrenoceptor agonists in gastric fundus and by the five agonists in duodenum. Furthermore, the relaxant responses to catecholamines and to beta3-adrenoceptor agonists were unaffected by the cyclic AMP-dependent protein kinase inhibitor, N-(2-[p-bromocinnamylamino]ethyl)-5-isoquinolinesulfonamide (H-89, 10 microM) in gastric fundus. These results suggest that beta3-adrenoceptor-induced relaxation is mediated through both cyclic AMP-dependent and cyclic AMP-independent pathways in gastric fundus and through a cyclic AMP-independent pathway in duodenum.

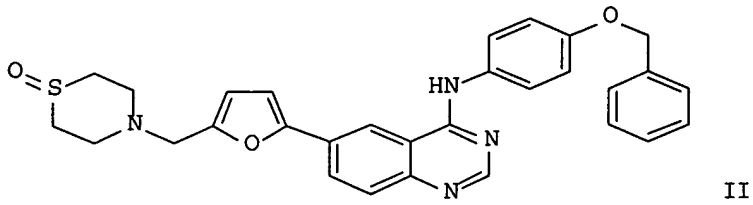
L7 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:854415 CAPLUS Full-text
DOCUMENT NUMBER: 133:362769
TITLE: Preparation of 6-(thiomorpholinomethylfuranyl)-4-quinazolinamines as protein tyrosine kinase inhibitors
INVENTOR(S): Carter, Malcolm Clive; Cockerill, George Stuart; Guntrip, Stephen Barry; Lackey, Karen Elizabeth; Smith, Kathryn Jane
PATENT ASSIGNEE(S): Glaxo Group Ltd., UK
SOURCE: Brit. UK Pat. Appl., 151 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
GB 2345486	A1	20000712	GB 1999-29973		19991217
PRIORITY APPLN. INFO.:			GB 1999-518	A	19990111
			GB 1999-15510	A	19990703

OTHER SOURCE(S): MARPAT 133:362769
GI



I



II

AB The title compds. (I) [wherein X = N or CH; V and Y = independently CR1, CR2, or N; and V ≠ Y; R1 = Q(CH2)qAr; m = 1 or 2; p = 1 or 2; q = 1-4; Ar = (un)substituted Ph, furanyl, thiophenyl, pyrrolyl, or thiazolyl; R2 = H, halo, OH, alkyl(amino) alkoxy, or dialkylamino; U = (un)substituted Ph, pyridyl, (benz)imidazolyl, (iso)indolyl, (iso)indolinyl, indazolyl, or benzotriazolyl] were prepared as protein tyrosine kinase inhibitors for the treatment of cancer and other disorders mediated by aberrant protein tyrosine kinase activity. For example, II•2HCl was formed in a multi-step sequence involving (1) reaction of 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan with (4-benzyloxyphenyl)(6-bromoquinazolin-4-yl)amine using Pd(PPh3)2Cl2 in dioxane, (2) conversion of the cyclic acetal to the aldehyde with HCl in THF, (3) addition of thiomorpholine-S-oxide in CH2Cl2 and conversion to the HCl salt. I inhibited EGFR and c-erbB-2 tyrosine kinase with IC50 < 0.10 μM and suppressed cell proliferation against a range of tumor cell lines.

L7 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER:	2001043156 MEDLINE Full-text
DOCUMENT NUMBER:	PubMed ID: 11011029
TITLE:	BRL37344, but not CGP12177, stimulates fuel oxidation by soleus muscle in vitro.
AUTHOR:	Board M; Doyle P; Cawthorne M A
CORPORATE SOURCE:	Clore Laboratory for Metabolic Research, University of Buckingham, Hunter Street, Buckingham MK18 1EG, UK.. mary.board@buckingham.ac.uk
SOURCE:	European journal of pharmacology, (2000 Oct 6) Vol. 406, No. 1, pp. 33-40. Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY:	Netherlands
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200012
ENTRY DATE:	Entered STN: 22 Mar 2001 Last Updated on STN: 22 Mar 2001 Entered Medline: 7 Dec 2000

AB The beta(3)-adrenoceptor agonist, (RR+SS)-(+/-)-4-[2-)2-)3-chlorophenyl)-2-hydroxyethyl)amino)propyl]ph enoxyacetate (BRL37344), stimulated fuel utilisation by isolated mouse soleus muscle at concentrations 10- to 100-fold lower than those required to stimulate lipolysis in brown adipocytes. At 1x10(-10) M BRL37344, uptake and phosphorylation of 2-deoxyglucose was increased (40%), as was glucose-oxidation (50%), palmitate-oxidation (70%) and oxidation of [2-14C]pyruvate (2-fold), indicating stimulation of tricarboxylic acid cycle reactions. Oxidation of [1-14C]pyruvate was unaffected, indicating no stimulation of pyruvate dehydrogenase activity. Other beta(3)-adrenoceptor agonists, disodium(RR)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]- 1,3-benzodioxazole-2,2-dicarboxylate (CL316,243, 1x10(-7) M) and (S)-4- 2-[2-hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl pheno xymeth ylcyclohexylphosphiric acid lithium salt (SB226552, 1x10(-9) M), achieved similar stimulation of 2-deoxyglucose uptake and phosphorylation but (+/-)-4-(3-t-butylamino-2-hydroxypropoxy)benzimidazol-2-one (CGP12177A) had no effect. The inhibitor of protein kinase A, H-89 (isoquinolinesulfonamide), had little effect on the stimulation of pyruvate-oxidation by BRL37344, while the specific inhibitor of protein kinase C, bisindolylmaleimide IX, reduced the stimulated rate to slightly below basal values. We consider that these responses provide evidence of the presence of a novel beta-adrenoceptor in skeletal muscle, which we have termed beta(skel)-adrenoceptor.

L7 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 97259590 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9105691
TITLE: Stimulation of cyclic AMP-dependent protein kinase in rat atria by (-)-CGP 12177 through an atypical beta-adrenoceptor.
AUTHOR: Kaumann A J; Lynham J A
CORPORATE SOURCE: Babraham Institute, Human Pharmacology Laboratory, Cambridge.
SOURCE: British journal of pharmacology, (1997 Apr) Vol. 120, No. 7, pp. 1187-9.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 9 Jul 1997
Last Updated on STN: 9 Jul 1997
Entered Medline: 24 Jun 1997
AB Mammalian hearts possess an atypical beta-adrenoceptor (non-beta 1, non-beta 2, non-beta 3) through which (-)-4-(3-t-butylamino-2 -hydroxypropoxy)benzimidazol-2-one ((-)-CGP 12177) causes cardiostimulant effects. Here we showed that (-)-CGP 12177 increased the activity of adenosine 3':5'-cyclic monophosphate (cyclic AMP)-dependent protein kinase in the presence of 200 nM (-)-propranolol in rat atria at a concentration (10 microM) that elicits maximum positive chronotropic and inotropic effects. The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (IBMX) potentiated the positive chronotropic and inotropic effects of (-)-CGP 12177. We suggest that the atypical beta-adrenoceptor is coupled positively to the Gs protein-adenylyl cyclase system.

L7 ANSWER 7 OF 10 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 95230578 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7536246
TITLE: Agonist-independent, muscle-type-specific signal transduction pathways in cat esophageal and lower esophageal sphincter circular smooth muscle.
AUTHOR: Sohn U D; Han B; Tashjian A H Jr; Behar J; Biancani P
CORPORATE SOURCE: Department of Medicine, Rhode Island Hospital and Brown Medical School, Providence, USA.
CONTRACT NUMBER: DK 11011 (NIDDK)
DK 28614 (NIDDK)
SOURCE: The Journal of pharmacology and experimental therapeutics, (1995 Apr) Vol. 273, No. 1, pp. 482-91.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505

ENTRY DATE: Entered STN: 24 May 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 17 May 1995

AB Smooth muscle cells isolated from the circular muscle layer of cat esophagus and lower esophageal sphincter (LES) exhibit distinct contractile intracellular signal transduction pathways in response to acetylcholine. To determine whether these contractile pathways are muscle type dependent, the authors examined the signal transduction pathways utilized by substance P and bombesin, which in other tissues, use different signal transduction pathways, and by the GTP analog, guanosine 5'-O-3-thiotriphosphate (GTP gamma S), which activates all available G proteins. Western blot analysis of esophageal and LES circular muscle revealed the presence of Gq-G11 (42 kD), Gi1-Gi2 (40 kD) and Go-Gi3 (40 kD) types of G proteins. The responses of esophageal cells to bombesin and substance P were blocked by 1) a Gi3 protein antibody, 2) the inhibitor of specific phosphatidylcholine-phospholipase C (PLC) D609 potassium tricyclo-[5.2.1.0(2.6)]-decyl-(9[8])-xanthogenate, 3) inhibition of phosphatidic acid phosphohydrolase by propranolol, 4) the protein kinase C inhibitor 1-(5-isoquinolinesulfonyl)- 2-methylpiperazine dihydrochloride (H7) and 5) incubation in Ca(++)-free medium. Conversely, the responses of LES muscle cells to bombesin and substance P were blocked by 1) a Gq-G11 antibody, 2) a phosphatidylinositol-specific PLC antagonist U-73122 (1-[6-[[17 beta-3-methoxyestra-1,3,5(10)-trien-17-yl]amino]hexyl]-1H-pyrrole-2,5- dione), 3) the calmodulin inhibitor CGS9343B (1,3-Dihydro-1-[1-((4-methyl-4H,6H-pyrrolo[1,2-a]-[4,1]benzoxazepin++ +-4 - yl)methyl-4-piperindinyl]-2H-benzimidazol-2-one maleate) and 4) incubation in Sr++. After permeabilization by saponin, inositol 1,4,5-trisphosphate contracted LES but not esophageal cells. The inositol 1,4,5-trisphosphate receptor antagonist heparin and depletion of intracellular Ca++ stores by thapsigargin or A23187 4- Benzoxazolecarboxylic acid, 5-(methylamino)-2-[[3,9,11-trimethyl-8-[1- methyl-2-oxo-2-(1H-pyrrol- 2-yl)ethyl]-1,7-dioxaspiro[5.5]undec-2- yl]methyl]-, [6s-[6α (2S*,3S*),8β (R*), 9β, 11. alpha.]]-(9Cl), blocked bombesin- and substance P-induced contraction of LES but not of esophageal muscle. In addition, contraction in response to GTP gamma S, which activates all G proteins, was blocked in esophageal cells by a Gi3-protein antibody, propranolol, D609 and H7. In LES muscle cells, the response to GTP gamma S was blocked by a Gq protein antibody, U-73122 and CGS934B. These data demonstrate that, in esophageal muscle, different agonists activate the same Gi3 protein, phosphatidylcholine- specific phospholipases and protein kinase C-dependent pathway.(ABSTRACT TRUNCATED AT 400 WORDS)

L7 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:549410 CAPLUS Full-text
DOCUMENT NUMBER: 121:149410
TITLE: Mechanism of desensitization of the cloned vasopressin V1a receptor expressed in Xenopus oocytes
AUTHOR(S): Nathanson, Michael H.; Burgstahler, Angela D.; Orloff, John J.; Mani, Arya; Moyer, M. Susan
CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SOURCE: American Journal of Physiology (1994), 267(1, Pt. 1), C94-C103
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The vasopressin V1a receptor exerts its effects by G protein-mediated increases in cytosolic Ca2+ (Cai2+) and activation of protein kinase C. The V1a receptor also undergoes autologous desensitization. To clarify the mechanism of this desensitization, the authors expressed the cloned receptor in Xenopus oocytes, and vasopressin-induced Cai2+ waves were examined as an index of V1a activation using confocal microscopy. Pretreatment of oocytes with a minimal concentration of vasopressin inhibited further generation of Cai2+ waves upon maximal stimulation. Such pretreatment did not abolish Cai2+ waves induced by subsequent microinjection of inositol trisphosphate, suggesting that this phenomenon represents receptor desensitization rather than depletion of inositol trisphosphate-sensitive Cai2+ stores. Pretreatment with phorbol dibutyrate, ionomycin, or 8-bromoadenosine 3',5'-cyclic monophosphate had no effect on vasopressin-induced Cai2+ waves. Oocytes recovered from desensitization within 1 h, but the microtubule inhibitor (methyl-5-[2-thienylcarbonyl]-1H-benzimidazol-2-yl)carbamate (nocodazole) inhibited this recovery. Receptor binding sites were reduced by over 50% within 10 min of exposure to vasopressin, with no associated change in the Kd for the V1a receptor. These findings indicate that 1) expression of the cloned V1a receptor in Xenopus oocytes, coupled with subcellular Cai2+ imaging, provides a useful system to examine mechanisms of V1a desensitization, 2) the V1a receptor undergoes autologous desensitization in this exptl. system, and 3) protein kinase C, Cai2+, and cAMP do not appear responsible for this desensitization, but 4) microtubule-dependent recycling of the receptor is preserved in this system and may be important for receptor desensitization.

L7 ANSWER 9 OF 10 MEDLINE on STN
ACCESSION NUMBER: 91025129 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2222519
TITLE: Modulation of doxorubicin-induced chromosomal damage by calmodulin inhibitors and its relationship to cytotoxicity in progressively doxorubicin-resistant tumor cells.
AUTHOR: Ganapathi R; Grabowski D; Hoeltge G; Neelon R
CORPORATE SOURCE: Division of Laboratory Medicine, Cleveland Clinic Foundation, OH 44195.
CONTRACT NUMBER: 2R01CA35531 (NCI)
SOURCE: Biochemical pharmacology, (1990 Oct 1) Vol. 40, No. 7, pp. 1657-62.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199011
ENTRY DATE: Entered STN: 17 Jan 1991
Last Updated on STN: 3 Feb 1997
Entered Medline: 8 Nov 1990

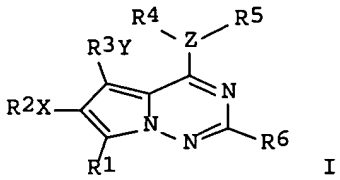
AB Modulation of doxorubicin (DOX) cytotoxicity by the calmodulin inhibitor trifluoperazine (TFP) in progressively doxorubicin-resistant L1210 mouse leukemia cells is unrelated to effects on drug accumulation. Based on the clastogenic activity of DOX, the effects of TFP and the selective calmodulin inhibitor 1,3-dihydro-1-[1-[4-methyl-4H,6H-pyrrolo[1,2-a][4,1]- benzoxazepin-4-yl- methyl]-4-piperidinyl]-2H-benzimidazol-2-o ne(1:1) maleate (CGS9343B) on DOX-induced chromosomal damage and its relationship to cytotoxicity were evaluated in sensitive and progressively DOX-resistant L1210 cells. Potentiation of DOX cytotoxicity by CGS9343B (a potent inhibitor of calmodulin which does not inhibit protein kinase C) was related to the level of resistance. Further, for equivalent cytotoxicity, cellular DOX levels in the absence versus the presence of TFP or CGS9343B were markedly higher. Exposure to calmodulin inhibitors following DOX treatment enhanced chromosomal aberrations and cytotoxicity. Maximal effects of calmodulin inhibitors were apparent when used during and after DOX treatment, and potentiation of cytotoxicity was related to modulation of DOX-induced chromosomal aberrations. Results suggest that inhibition of calmodulin-regulated processes is a potential target in the modulation of DNA damage/repair, and could play a pivotal role in the expression of "acquired resistance" to DOX.

L7 ANSWER 10 OF 10 MEDLINE on STN
ACCESSION NUMBER: 87201466 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3033469
TITLE: CGS 9343B, a novel, potent, and selective inhibitor of calmodulin activity.
AUTHOR: Norman J A; Ansell J; Stone G A; Wennogle L P; Wasley J W
SOURCE: Molecular pharmacology, (1987 May) Vol. 31, No. 5, pp. 535-40.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198706
ENTRY DATE: Entered STN: 3 Mar 1990
Last Updated on STN: 3 Mar 1990
Entered Medline: 18 Jun 1987

AB 1,3-Dihydro-1-[1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]- benzoxazepin-4-yl)methyl]-4-piperidinyl]-2H-benzimidazol-2-o ne (1:1) maleate was synthesized in six steps from methyl anthranilate and designated CGS 9343B. CGS 9343B inhibited calmodulin-stimulated cAMP phosphodiesterase activity with an IC50 value of 3.3 microM. CGS 9343B was 3.8 times more potent than trifluoperazine (IC50 = 12.7 microM) as an inhibitor of calmodulin activity. CGS 9343B did not inhibit protein kinase C activity at concentrations up to 100 microM, whereas trifluoperazine inhibited protein kinase C activity with an IC50 value of 43.9 microM. CGS 9343B weakly displaced [3H]spiperone from postsynaptic dopamine receptors with an IC50 value of 4.8 microM while the value for trifluoperazine, a potent antipsychotic agent, was 0.018 microM. It is concluded that CGS 9343B is a novel, potent, and selective inhibitor of calmodulin activity. Unlike trifluoperazine, CGS 9343B does

not inhibit protein kinase C activity and does not possess potential antidopaminergic activity.

```
=> s azaindol and kinase and inhibitor
L8            0 FILE MEDLINE
L9            6 FILE CAPLUS

TOTAL FOR ALL FILES
L10           6 AZAINDOL AND KINASE AND INHIBITOR

=> d ibib abs 1-6

L10  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:80698  CAPLUS Full-text
DOCUMENT NUMBER:          140:146173
TITLE:                    Preparation of pyrrolotriazines as selective VEGFR-2
                          and FGFR-1 kinase inhibitors for
                          treatment of proliferative diseases
INVENTOR(S):              Bhide, Rajeev; Ruel, Rejean; Thibeault, Carl;
                          L'heureux, Alexandre
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
SOURCE:                   PCT Int. Appl., 66 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    -------------------      --------
     WO 2004009601         A1    20040129    WO 2003-US22554          20030718
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2492665            AA    20040129    CA 2003-2492665          20030718
     AU 2003254017         A1    20040209    AU 2003-254017           20030718
     US 2004063707         A1    20040401    US 2003-622593           20030718
     US 6969717            B2    20051129
     US 2004072832         A1    20040415    US 2003-623171           20030718
     US 6869952            B2    20050322
     EP 1539763            A1    20050615    EP 2003-765754           20030718
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     CN 1681818            A     20051012    CN 2003-821820           20030718
     CN 1681508            A     20051012    CN 2003-821915           20030718
     JP 2005538990         T2    20051222    JP 2004-523591           20030718
     US 2005124621         A1    20050609    US 2005-35248            20050113
     NO 2005000417         A     20050217    NO 2005-417              20050125
     US 2006058304         A1    20060316    US 2005-214267           20050829
PRIORITY APPLN. INFO.:                        US 2002-397256P      P  20020719
                                              US 2003-447213P      P  20030213
                                              US 2003-622593       A3 20030718
                                              US 2003-623171       A1 20030718
                                              WO 2003-US22554      W  20030718
OTHER SOURCE(S):          MARPAT 140:146173
GI
```



I

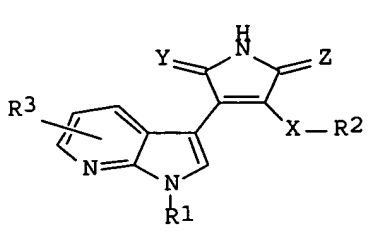
AB Title compds. I [Z = O, S, N, etc.; X, Y = O, OCO, S, etc.; R1 = H, CH3, OH, etc.; R2, R3 = H, (un)substituted alkyl, alkenyl etc.; R4 = (un)substituted 7-azaindolyl, e.g., F, Cl, Me; R5 = H, absent when Z = O, S; R6 = H, (un)substituted alkyl, aryl, etc.] and their pharmaceutically acceptable salts were prepared For example, electrophilic substitution of compound I [R1 = H; R2X = benzyloxy; R3Y = CH3; ZR5R6 = Cl] with 4-fluoro-5-hydroxy-7-azaindole, e.g., prepared from 4-chloro-1H-pyrrolo[2,3- b]pyridine in 6-steps, afforded compound I [R1 = H; R2X = benzyloxy; R3Y = CH3; ZR5R6 = 4-fluoro-7-azaindol-5-yloxy] in 80% yield. In VEGFR-2 and FGFR-1 kinase assays, 38-examples of compds. I exhibited IC50 values ranging from 0.001-10 μM. Of note, pyrrolotriazines I exhibited selective VEGFR-2 and FGFR-1 kinase inhibition (no data provided). Compds. I are claimed useful for the treatment of cancer, inflammation, autoimmune diseases.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

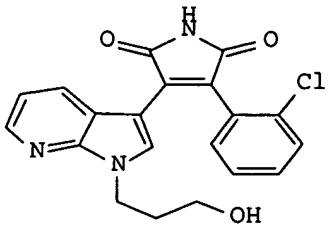
L10 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:913164 CAPLUS Full-text
DOCUMENT NUMBER: 139:395805
TITLE: Substituted pyrroline kinase inhibitors, particularly 3-substituted-4-[1-(3-hydroxypropyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-1H-pyrrole-2,5-diones and analogs with activity against GSK-3 and PKC, and their preparation, pharmaceutical compositions, and use.
INVENTOR(S): Zhang, Han-Cheng; Kuo, Gee-Hong; Maryanoff, Bruce E.; Ye, Hong; O'Neill, David; Shen, Lan; Demarest, Keith; Conway, Bruce; Mccomsey, David F.
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
SOURCE: PCT Int. Appl., 155 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003095452	A1	20031120	WO 2003-US14113		20030506
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2003225295	A1	20031111	AU 2003-225295		20030506
CA 2485527	AA	20031120	CA 2003-2485527		20030506
US 2004006095	A1	20040108	US 2003-430000		20030506
EP 1506192	A1	20050216	EP 2003-722017		20030506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2005529918	T2	20051006	JP 2004-503468		20030506
PRIORITY APPLN. INFO.:			US 2002-378503P	P	20020508
			WO 2003-US14113	W	20030506

OTHER SOURCE(S): MARPAT 139:395805
GI



I



II

AB The invention is directed to novel substituted pyrroline compds., specifically compds. I, useful as kinase inhibitors, and methods for treating or ameliorating kinase-mediated disorders using I [wherein R1 = H, variety of sidechains containing ethers, amines, (hetero)aromatic rings, etc.; X = bond, alkyl, alkenyl, alkynyl; R2 = cycloalkyl, heterocyclyl, aryl, heteroaryl; or XR2 = cyano; R3 = H, 1-3 optional substituents; Y, Z = O, S, (H,OH), (H,H); provided that at least one of Y and Z is O]. Compds. I are especially useful as inhibitors of protein kinase C (including α, β-I, β-II, and γ isoforms) and glycogen synthase kinase 3 (including GSK-3β). As such, I are claimed useful for treatment of a wide variety of cardiovascular diseases, diabetes and associated disorders, inflammatory diseases, immunol. disorders, dermatol. disorders, oncol. disorders, and CNS disorders. Approx. 80 compds. I and salts were prepared, and the free bases are claimed as a table. For instance, 7-azaindole was metalated with EtMgBr and acylated with ClCOCO2Me to give RCOCO2Me (R = 7- azaindol-3-yl). This compound was N1-alkylated with Br(CH2)3OSiMe2Bu-tert, then cyclocondensed with 2-ClC6H4CH2CONH2 in the presence of KOBu-tert, and deprotected with HCl, to give title compound II. In tests against rabbit recombinant GSK-3β, II had IC50 values of 0.009-0.010 μM. Against isoenzymes of PKC at 1 μM, II had inhibitions as follows: α 18%, β-II 14%, and γ 48%.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:851162 CAPLUS Full-text
DOCUMENT NUMBER: 136:6198
TITLE: Neuroprotective and anti-proliferative analogs of staurosporine and granulatimide, namely 3-(1H-indol-3-yl)-1H-pyrrole-2,5-diones, 3-(1H-indol-3-yl)-4-(1H-indol-1-yl)-1H-pyrrole-2,5-diones, and pyrrolo-β-carboline derivatives, and their preparation and use as modulators of apoptosis
INVENTOR(S): Jaquith, James B.; Fallis, Alex; Gillard, John
PATENT ASSIGNEE(S): Aegera Therapeutics Inc., Can.
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087887	A2	20011122	WO 2001-CA718	20010518
WO 2001087887	A3	20020228		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2308994	AA	20011119	CA 2000-2308994	20000519
CA 2409355	AA	20011122	CA 2001-2409355	20010518
EP 1283836	A2	20030219	EP 2001-935858	20010518
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004509068	T2	20040325	JP 2001-584281	20010518
US 2004220202	A1	20041104	US 2003-637599	20030811
US 2004102467	A1	20040527	US 2003-276803	20031023
PRIORITY APPLN. INFO.:			CA 2000-2308994 A	20000519
			WO 2001-CA718 W	20010518

OTHER SOURCE(S): MARPAT 136:6198
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention features 3-(1H-indol-3-yl)-4-(1H-indol-1-yl)-1H-pyrrole-2,5- diones of formula I, ring-substituted pyrrolo-β-carboline derivs. of formula II, and 3-(1H-indol-3-yl)-1H-pyrrole-2,5-diones of formula III, which are useful as neuroprotective and anti-proliferative compds. [wherein: A1, B1 = H, alkyl; A2, B2 = H, OH or ethers, SH or thioethers; or A1A2 or B1B2 = oxo; or B1B2 = thioxo in III; X1-3 = C, N; X4 = CH or N; only 0-2 of X1-4 = N; X5 = N, C, S, or CH; X6-8 = C, N; X9 = CH or N; only 0-2 of X6-9 = N; R1-3, R6-8 = lone pair or oxido when bound at X = N, otherwise = H, (un)substituted alkyl, halo, N3, cyano, NO2, NH2 or derivs., OH or derivs., SH or derivs., C.tplbond.CH or derivs.; R4, R5 = H, wide variety of linear and substituted sidechains, possibly including amino acid or sugar residues; or R4R5 form a ring; Y = H, halo, OH, or alkyl]. Also disclosed are methods for the preparation of these compds., selected biol. profiles and uses of these compds. in the treatment of various neurodegenerative and inflammatory diseases of the human nervous system, and in the treatment of various other proliferative disorders characterized by loss of growth or cellular differentiation control including, but not limited to, cancer and inflammation. Over 100 compds. were prepared and individually claimed. A variety of bioassays were performed on selected compds. For instance, 5-methoxyindole was treated with oxalyl chloride and then aqueous ammonium carbonate to give 5-methoxy-α-oxoindole-3-acetamide (IV). In a sep. reaction, indole was N-alkylated with BrCH2CO2Et using KOBu-tert in THF, and the product was cyclized with IV in situ, to give title compound V. Cyclization of V using Me3SiOSO2CF3 in CH2Cl2 with concomitant oxidation over 3 days gave title compound VI. Both V and VI inhibited killing of mouse cerebral granule neurons by cisplatin in vitro, with an identical IC50 value of 10 μM. Biol. results suggest that the compds. prevent cell death by interfering with the apoptotic cascade at a point upstream of the caspases, i.e., the inhibition of one or several of the serine/threonine protein kinases directly upstream of the caspases. The compds. did not, however, significantly protect cancer cells from apoptosis. Furthermore, selected compds. down-regulated endogenous levels of HIAP1 mRNA in the neuroblastomal cell line LAN5, and thus represented new chemotherapeutics for treatment of cancer.

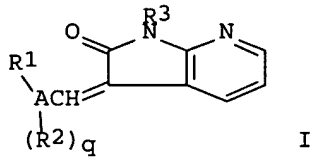
L10 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:467094 CAPLUS Full-text
DOCUMENT NUMBER: 125:114586
TITLE: Preparation of substituted 3-arylidene-7-azaoxindoles as tyrosine kinase inhibitors
INVENTOR(S): Buzzetti, Franco; Brasca, Gabriella Maria; Longo, Antonio; Ballinari, Dario
PATENT ASSIGNEE(S): Pharmacia S.P.A., Italy
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9616964	A1	19960606	WO 1995-EP4247	19951030
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

CA 2180730	AA	19960606	CA 1995-2180730		19951030
AU 9539262	A1	19960619	AU 1995-39262		19951030
EP 741726	A1	19961113	EP 1995-937030		19951030
EP 741726	B1	19991117			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE					
CN 1139929	A	19970108	CN 1995-191374		19951030
HU 74875	A2	19970228	HU 1996-2357		19951030
JP 09508924	T2	19970909	JP 1995-518113		19951030
AT 186727	E	19991215	AT 1995-937030		19951030
ES 2140717	T3	20000301	ES 1995-937030		19951030
ZA 9509927	A	19960610	ZA 1995-9927		19951122
US 5719135	A	19980217	US 1996-669315		19960709
NO 9603066	A	19960723	NO 1996-3066		19960723
FI 9602954	A	19960724	FI 1996-2954		19960724
GR 3032535	T3	20000531	GR 2000-400231		20000202
PRIORITY APPLN. INFO.:			GB 1994-23997	A	19941128
			WO 1995-EP4247	W	19951030

OTHER SOURCE(S): CASREACT 125:114586; MARPAT 125:114586

GI



I

AB The preparation of substituted 3-arylidene-7-azaoxindoles I [A = benzene, naphthalene, 5,6,7,8-tetrahydronaphthalene, quinoline, isoquinoline, indole or 7-azaindole rings; R1 = H, CN, various sulfates and sulfonamides, CO2R6, CONHCH2(CHOH)nCH2OH, various amides, NR7R8, N(CH2CH2OH)2, NHCH2(CH(OH))nCH2OH, NHCONH2, NHC(NH2):NH, NHCO(CH(OH))nCH2OH, NHSO2R9, OR10, OCH2(CH(OH))nCH2OH, OOC(CH(OH))nCH2OH, OPO(OH)2, CH2NH2, C(NH2):NH, CH2NHC(NH2):NH, CH2OH, CH2OOC(CH(OH))nCH2OH, CH2OPO(OH)2, PO(OH)2, etc.; R2 is C1-6 alkyl, halo, or OH; R3 = H or C1-6 alkyl; R4 = H, C1-6 alkyl or CH2(CH(OH))nCH2OH; R5 = H, C1-6 alkyl, CH2(CH(OH))nCH2OH or (CH2)mNMe2; R6 = H, C1-6 alkyl or CH2(CH(OH))nCH2OH; each of R7 and R8 independently is H or C1-6 alkyl; R9 = Me or tolyl; R10 = H, C1-6 alkyl or C2-6 alkanoyl; Z = CH2, O, NH or NCH2CH2OH; n = 0, 1; m = 2, 3; p = 1-3; q = 0-2] are described, and their pharmaceutically acceptable salts, for use as tyrosine kinase inhibitors . A variety of processes are claimed for the preparation of I, including: (a) condensation of an aldehyde with an azaoxindole, (b) subjecting an amino-substituted 3-arylidene-7-azaoxindole to N-alkylation, N-acetylation, N-sulfonylation, N-amidation, or N-carbamoylation, (c) subjecting a hydroxy-substituted 3-arylidene-7-azaoxindole to O-alkylation, O-acylation, or O-phosphorylation, (d) esterification of a carboxy-substituted 3-arylidene-7-azaoxindole, (e) ammonia addition to a cyano-substituted 3-arylidene-7-azaoxindole, and (f) amination of a chloromethyl-substituted 3-arylidene-7-azaoxindole. As an example of the condensation reaction, 7-azaoxindole was refluxed with 3,5-di-tert-butyl-4-hydroxybenzaldehyde in EtOH with added piperidine for 3 h to give 3-[(3,5-di-tert-butyl-4-hydroxyphenyl)methylene]-7-azaoxindole in 80% yield. Another compound, 3-[(7-azaindol -3-yl)methylene]-7-azaoxindole, exhibited inhibitory activity for the in vitro p45 v-abl kinase assay (IC50 = 1.05 μM) and for the in vivo human chronic myeloid leukemia K562 cell growth inhibition assay (IC50 = 3.89). Pharmaceutical formulations of compds. I are claimed (2 examples).

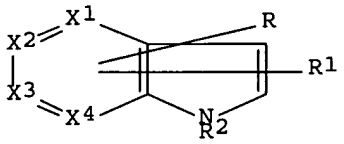
L10 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1996:209666 CAPLUS Full-text
DOCUMENT NUMBER:	124:260834
TITLE:	Preparation and formulation of substituted azaindolylidene compounds as tyrosine kinase inhibitors
INVENTOR(S):	Buzzetti, Franco; Brasca, Gabriella Maria; Longo, Antonio; Ballinari, Dario
PATENT ASSIGNEE(S):	Pharmacia S.P.A., Italy
SOURCE:	PCT Int. Appl., 64 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9600226	A1	19960104	WO 1995-EP2043	19950530
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2168659	AA	19960104	CA 1995-2168659	19950530
AU 9526716	A1	19960119	AU 1995-26716	19950530
EP 715628	A1	19960612	EP 1995-921777	19950530
EP 715628	B1	20021002		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
CN 1129941	A	19960828	CN 1995-190567	19950530
HU 74609	A2	19970128	HU 1996-729	19950530
JP 09502457	T2	19970311	JP 1995-502741	19950530
AT 225348	E	20021015	AT 1995-921777	19950530
PT 715628	T	20030228	PT 1995-921777	19950530
ES 2186721	T3	20030516	ES 1995-921777	19950530
JP 3773257	B2	20060510	JP 1996-502741	19950530
ZA 9505223	A	19960131	ZA 1995-5223	19950623
US 5663346	A	19970902	US 1996-592297	19960209
FI 9600751	A	19960219	FI 1996-751	19960219
NO 9600713	A	19960222	NO 1996-713	19960222
PRIORITY APPLN. INFO.:			GB 1994-12719 A	19940624
			WO 1995-EP2043 W	19950530

OTHER SOURCE(S): MARPAT 124:260834
GI



I

AB The title compds. I [one of X1 , X2, X3, X4 is N and the others are CH; R is CH:C(CN)CONH2, etc.; R1 is hydrogen, amino, carboxy, cyano, etc.; R2 is H, C1-C6 alkyl, etc.; a proviso is given] are prepared 5-Cyano-3-[(7- azaindol-3-yl)methylen]-2-oxindole (NMR data given) in vitro showed IC50 of 0.98 mM against p-45 v-abl kinase.

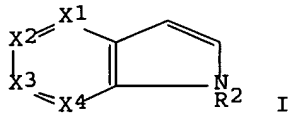
L10 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:557633 CAPLUS Full-text
DOCUMENT NUMBER: 121:157633
TITLE: Preparation and formulation of azaindoles as tyrosine kinase inhibitors
INVENTOR(S): Buzetti, Franco; Crugnola, Angelo; Ballinari, Dario; Greco, Felicita
PATENT ASSIGNEE(S): Farmitalia Carlo Erba S.R.L., Italy
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9414808	A1	19940707	WO 1993-EP3536	19931215
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN,				

MW, NO, NZ, PL, RO, RU, SK, UA, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

CA 2126228	AA	19940707	CA 1993-2126228		19931215
AU 9458105	A1	19940719	AU 1994-58105		19931215
AU 670488	B2	19960718			
EP 626963	A1	19941207	EP 1994-903774		19931215
EP 626963	B1	19990609			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE					
HU 67431	A2	19950428	HU 1994-1950		19931215
JP 07504208	T2	19950511	JP 1994-514761		19931215
JP 3507497	B2	20040315			
AT 181074	E	19990615	AT 1994-903774		19931215
ES 2134926	T3	19991016	ES 1994-903774		19931215
IL 108087	A1	19970930	IL 1993-108087		19931220
ZA 9309578	A	19940811	ZA 1993-9578		19931221
CN 1093707	A	19941019	CN 1993-112970		19931222
US 5397787	A	19950314	US 1993-171154		19931222
FI 9403838	A	19940819	FI 1994-3838		19940819
PRIORITY APPLN. INFO.:			GB 1992-26855	A	19921223
			WO 1993-EP3536	W	19931215

OTHER SOURCE(S): MARPAT 121:157633
GI



I

AB Title compds. [I; R2 = H, alkyl, alkanoyl; 1 of X1-X4 = N and the others are CH; any C may be substituted by R or R1; R = CH:C(CN)R6, (un)substituted 2-oxo-3-indolylidenemethylene; R1 = H, halo, alkyl(oxy), NO2, (di)(alkyl)amino; R6 = CONH2, CONH(CH2)nPh, CSNH2, cyano; n = 0-5] were prepared Thus, 7-azaindole was formylated and the product refluxed with 2-oxindole in EtOH containing piperidine to give (Z)-3-[(7- azaindol-3-yl)methylene]-2-oxindole which had IC50 of 0.05 μM against p45 v-abl kinase in vitro.

=> log y